

Domination of Gastric Complications Among Diabetic Patients

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ABSTRACT

This letter covers the epidemiology, pathophysiology/complications and management of diabetic gastroparesis (DGP), and more broadly diabetic gastroenteropathy, which encompasses all the gastrointestinal manifestations of diabetes mellitus (DM). Hyperglycemia, autonomic neuropathy, and enteric neuromuscular inflammation and injury are implicated in the pathogenesis of delayed gastric emptying (GE). Initial options include dietary modifications, supplemental oral nutrition, and antiemetic and prokinetic medications. Patients with more severe symptoms may require a venting gastrostomy or jejunostomy and/or gastric electrical stimulation (GES). To date, few population-based studies have estimated the true prevalence and incidence of gastroparesis. Nonetheless, its prevalence appears to be rising, as does its incidence

among minority populations, documented via hospitalizations, which can impose significant economic burdens on patients.

Key words: Gastroparesis; Pyloric dysfunction; Diabetes; Delayed gastric emptying; Dyspepsia; Gastric electrical stimulation

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Abbreviations

Diabetes Mellitus (DM); Gastric Emptying (GE); Gastroparesis (GP); Diabetic Gastroparesis (DGP); Gastroesophageal Reflux Disease (GERD); Functional Dyspepsia (FD); Gastric Electrical Stimulation (GES); High-Frequency Stimulation (HFS); Randomized Controlled Trials (RCTs); Idiopathic Gastroparesis (IGP)

LETTER TO THE EDITOR

Up to 50% of patients with type 1 and 2 diabetes mellitus (DM) and suboptimal glycemic control have delayed GE, which can be documented with scintigraphy, 13 C-breath tests, or a wireless motility capsule; the remainder have normal or rapid GE^[1-3]. Also, it has been determined that 29% of patients with GP had diabetes mellitus^[4], 13% developed symptoms after gastric surgery and 36% were idiopathic. About 12% of global health care expenditure (\$727 billion) is spent on diabetes. When expanded to the age group between 18 and 99 years, the cost would total to \$850 billion. In conjunction with the rising prevalence, the cost is expected to rise to a staggering \$958 billion by 2045. In the USA, an estimated 5 million patients suffer from some form of GP, and the female: male ratio is 4:1. Many patients with delayed GE are asymptomatic; others have dyspepsia (i.e., mild-moderate indigestion, with or without a mild delay in GE) or GP, which is a syndrome characterized by moderate-severe upper gastrointestinal symptoms and delayed GE that suggest, but are not accompanied by, gastric outlet obstruction^[5]. GP can markedly impair quality of life and up to 50% of patients have significant anxiety and/or depression^[1,6-8]. Woodhouse et al, 2017

reported combined anxiety/ depression in 24%, severe anxiety in 12%, depression in 23%, and somatization in 50%^[6]. In diabetic patients (without neuropathy) and healthy controls, acute hyperglycemia will instead relax the proximal stomach, and suppress gastric electrical activity (e.g., reduced the frequency, propagation, and contraction of the antrum) in both fasting and post-prandial conditions, thereby slowing gastric emptying^[9]. Abdominal pain is often epigastric (43%), postprandial (72%), nocturnal (74%), and frequently associated with interference with sleep (66%)^[7]. Early satiety (88%), and bloating (64%) were the most common symptoms, however 94% of patients had resolution of their symptoms a year after their operation^[10]. Severe/very severe upper abdominal pain occurred in 34% of GP patients and associated with other GP symptoms, somatization, and opiate medication use^[11]. Nausea and vomiting are more common in DGP whereas abdominal pain and early satiety are more frequent in idiopathic GP. The 3 main causes of GP are diabetic, postsurgical, and idiopathic^[12]. Although DP is frequently associated with diabetes (DGP), idiopathic gastroparesis (IGP) accounts for the majority of cases (60%)^[13]. In diabetes, measuring gastric emptying has an additional justification in determining the absorption of orally administered drugs and nutrients, and thus post-prandial glucose regulation. Indeed, new onset or worsening of existing difficulties in blood glucose regulation may be the first symptom of DGP^[2]. Growing clinical evidence shows that delayed GE (in GP patients) may be a factor associated with severe reflux, dyspepsia, or both. GP, concomitant in 25% of patients with GERD, has been shown to improve after Nissen fundoplication^[14]. Treatment consists of a combination of lifestyle and dietary medication, medications (antiemetics, prokinetics, neuromodulators, and accommodation-enhancers), alternative and complementary therapy, endoscopic therapy (pyloric-directed therapy, temporary stimulation, jejunostomy, or venting gastrostomy) and surgical therapy (pyloroplasty, gastric electrical stimulation, gastrectomy)^[15]. In patients with GP, etiologies, symptom severity, and treatments vary among races and ethnicities and between sexes^[16]. If a doctor suspects a person with diabetes has GP, he will typically order one or more of the following tests to confirm the diagnosis: Barium X-ray; Barium beefsteak test; Radioisotope gastric-emptying scan; Gastric manometry Blood tests to check for nutritional deficiencies and electrolyte imbalances that are common with GP; Imaging of the gallbladder, kidneys, and pancreas to rule out gallbladder problems, kidney disease, or pancreatitis as causes; An upper endoscopy to check for abnormalities in the structure of the stomach^[17]. It is critical to clearly distinguish patients with functional dyspepsia (FD) from those with GP and to better understand the relationship among alterations in specific symptoms, GE, and altered peripheral and central sensory responses to gastric stimuli^[18]. Placebos have been tested in comparison to treatments for GP; however, results general are mixed. For example, Brewer et al, 2019 reported that RCTs on drug treatments have found placebos can marginally improve overall GP-related symptom scores but placebo effects did not improve gastric emptying^[19]. A similar situation may occur in a misguided attempt to improve gastric health by using the ubiquitously prescribed proton pump inhibitors, H2 receptor antagonists, and sucralfate or aluminum hydroxide-based antacids. These drugs are a cause of delayed gastric emptying. Such “therapeutic adventures”, akin to a pyromaniac leading a firefighting operation, may harm rather than improve DGP. A combination of acid-suppressing and prokinetic drugs is indicated only if dyspepsia and GP co-exist with each other^[20]. Vagal dysfunction has also been postulated to play a role in DGP. When food is ingested and gastric accommodation is impaired,

patients may experience symptoms such as early satiation, fullness and discomfort. Animal and human data suggest that vagal neuropathy can lead to reduction in pyloric relaxation, impaired antral contraction and disturbed antro-pyloric coordination^[21]. GP has also been associated with bronchiectasis, aspiration and chronic rejection. GI bleeding secondary to severe refractory esophagitis with an eventual necessity for surgery has also been reported^[22]. Most patients respond to conservative treatment with frequent small meals and an upright eating position, in combination with motility agents, such as oral erythromycin analogs, metoclopramide, and domperidone (the last of these is not FDA approved in the US^[23,24]. Metoclopramide and domperidone, a D2 dopamine receptor antagonist, are the most widely used but only metoclopramide is FDA approved in the US while domperidone is available in Europe, Canada, Mexico, and New Zealand^[25]. Metoclopramide acts on several different receptors; primarily as a dopamine receptor antagonist, both peripherally improving gastric emptying, and centrally resulting in an anti-emetic effect^[26,27]. Metoclopramide side effects, mostly related to its ability to cross the blood-brain barrier, include drowsiness, restlessness, hyperprolactinemia, and tardive dyskinesia (TD) (when taken more than 12 wk), a movement disorder that may be irreversible^[28-30]. Other groups of medication, such as 5-HT3 receptor antagonists, phenothiazines, and muscarinic cholinergic receptor antagonist, have been used off-label for symptomatic relieve but they do not have effect of gastric motility. While medications and dietary modification are the first line treatment, approximately 30% of patients do not respond to conservative management. These limitations of medical therapy highlight the need for an alternate therapeutic option^[31-35]. Traditional therapy for delayed gastric emptying has focused on supportive treatment, and there is no significant effective therapy. Low-energy shock wave can increase gastric contraction and emptying by activating axonal regeneration and increasing myenteric plexus, but not related with motility peptides^[3,36-38]. Gastric electrical stimulation (GES) (Enterra, Medtronic, Inc.) was approved by FDA in 2000 as a Humanitarian Use Device for patients with refractory diabetic or idiopathic GP^[39-41]. On the other hand, high-frequency stimulation (HFS) has no effect on gastric emptying but is able to significantly reduce symptoms of nausea and vomiting in gastroparetic patients^[42,43]. Compared to the use of single point electrodes, the use of two low-resolution electrodes allows recording gastric electrical wave propagation with greater detail. Low resolution recording appears to be superior to single point recordings, while awaiting practical high-resolution recordings^[44]. Abell et al, 2019 concluded that electrical stimulation improves symptoms and physiology with (1) an early and sustained anti-emetic effect; (2) an early and durable gastric prokinetic effect in delayed emptying patients; (3) an early anti-arrhythmic effect that continues over time; (4) a late autonomic effect; (5) a late hormonal effect; (6) an early anti-inflammatory effect that persists; and (7) an early and sustained improvement in health-related quality of life^[45]. GES improved symptoms in 75% of patients with 43% being at least moderately improved. Nausea, loss of appetite, and early satiety responded the best^[46,47]. Pain management is essential, as nearly 90% of patients report symptoms of epigastric pain^[22]. Pyloric dysfunction has been described in a subset of patients with GP, prompting experimentation with botulinum toxin injections into the pylorus, which is relatively safe and has been successfully used in other gastrointestinal disorders^[48]. The measurement of GE using a precise technique such as scintigraphy, which remains as the gold standard, nonetheless provides important mechanistic information when considering the effects on nutrient absorption,

postprandial glycemic responses in diabetes, or potential tachyphylaxis^[49]. Advances to better understand the pathophysiology and management of DGP have been limited, especially with discordance between symptoms and severity of delay in gastric emptying. Established treatment options are limited; however, recent pharmacologic and surgical interventions show promise^[50].

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